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The associations between parity, other reproductive factors and cartilage in women aged 50–80 years

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SUMMARY

Objective: Sex hormones and reproductive factors may be important for osteoarthritis (OA). The aim of this study was to describe the associations of parity, use of hormone replacement therapy (HRT) and oral contraceptives (OCs) with cartilage volume, cartilage defects and radiographic OA in a population-based sample of older women.

Design: Cross-sectional study of 489 women aged 50–80 years. Parity, use of HRT and OC was assessed by questionnaire; knee cartilage volume and defects by magnetic resonance imaging and knee joint space narrowing (JSN) and osteophytes by X-ray.

Results: Parity was associated with a deficit in total knee cartilage volume [adjusted $\beta = -0.69$ ml, 95% confidence interval (CI) −1.34, −0.04]. Increasing parity was associated with decreasing cartilage volume in both the tibial compartment and total knee (both P trend <0.05). Parity was also associated with greater cartilage defects in the patella compartment [adjusted odds ratio (OR) = 2.87, 95% CI = 1.39, 5.93] but not other sites. There was a consistent but non-significant increase in knee JSN (OR = 2.78, 95% CI = 0.75, 10.31) and osteophytes (OR = 1.69, 95% CI = 0.59, 4.82) for parous women. Use of HRT and/or OC was not associated with cartilage volume, cartilage defects or radiographic change.

Conclusions: Parity (but not use of HRT or OC) is independently associated with lower cartilage volume primarily in the tibial compartment and higher cartilage defects in the patella compartment in this population-based sample of older women.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and a major contributor to functional impairment and reduced independence in older people[1–3]. Female gender has been identified as a consistent risk factor for hand and knee OA[4]. The mechanism of gender disparity is unclear; however, it may involve less cartilage development during childhood, a higher rate of cartilage loss after menopause and greater worsening of cartilage defects over time[5]. In addition, body mass index (BMI) appears to be more strongly associated with both cartilage defects and tibial bone area in women[5] suggesting they are more susceptible to a raised BMI. While sex hormones are presumed to explain some of the sex differences, there is no consensus on the role of these factors in OA, with protective effects[6], no significant effects[7,8] and even worsening effects[9–11] being reported. Reproductive factors, particularly parity, may also be important due to alterations in sex hormones and weight changes during pregnancy and the postpartum period[12,13]. However, there have been only limited studies examining the associations between parity and OA including joint replacement and these again present conflicting results[9,14–20]. The association between us of oral contraceptive (OC) and OA has not been extensively studied[6] but the use of OCs appears protective for bone mass and vertebra deformities in this sample[21].

Cartilage loss is the cardinal feature of OA[22,23]. Radiography is regarded as the gold standard to assess cartilage loss but this technique has been criticized as insensitive due to its two-dimensional nature, measurement error and semi-quantitative assessment[24]. Magnetic resonance imaging (MRI) can directly visualize knee structure including cartilage volume, cartilage defects and subchondral bone size. However, there have been no studies that have investigated the associations between parity and

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knee cartilage though several studies have explored the effect of estrogen replacement therapy (ERT)[25–27]. Therefore, the aim of this cross-sectional study was to describe the associations between parity, use of hormone replacement therapy (HRT) and OCs and knee cartilage volume, cartilage defects, and radiographic OA in a population-based sample of older women.

Materials and methods

Subjects

This study used data from the Tasmanian Older Adult Cohort (TASOAC) study which is an ongoing prospective study in southern Tasmania, Australia. Its primary aims were to determine the environmental, genetic and biochemical factors associated with the development and progression of OA and osteoporosis. A total of 1,100 participants aged 50–80 years were randomly selected using computer-generated random numbers from the roll of electors in southern Tasmania, a comprehensive population listing, with an equal number of men and women selected. Baseline measurements were collected from April 2002 to September 2004. Participants were excluded if they were institutionalized, had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filings in the eye, and claustrophobia). All participants provided written informed consent and the study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee. The current study refers to women only.

Reproductive factors and other characteristics

Women's reproductive history was assessed by self-administered questionnaire. Parity was defined based on the women's live or still births and then categorized as follows (1 = nulliparous, 2 = one to two children, 3 = three to four children, and 4 = five or more) to ensure similar proportions in each group. Ever use and duration of OC use, current use of HRT and ever use and duration of use of HRT were also assessed by questionnaire. Years of use of OC and HRT were categorized as less than 5 years and 5 years or greater. Other reproductive factors included age at menarche, breastfeeding, menopause, and hysterectomy. The highest education level and employment status were assessed by questionnaire. Physical activity as mean steps per day was assessed by HJ-002 pedometer (Omron, Tokyo, Japan) as previously described[28].

Knee pain was assessed by self-administered questionnaire (WOMAC)[29]. Five categories of pain (walking on flat surface, going up/down stairs, pain at night, sitting/lying, and standing upright) were assessed separately with a 10-point scale from 0 (no pain) to 9 (most severe pain) for each category. A total pain score can range from 0 to 45. A history of knee surgery was assessed by the questionnaire and defined as a dichotomized variable. Hand OA was assessed by hand photographs[15] and presence of hand OA was defined if women had at least one Heberden's node (NH) in either hand.

Height was measured to the nearest 0.1 cm (with shoes, socks and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Delta Model 707; Hamburg, Germany) that was calibrated using a known weight at the beginning of each clinic. BMI was calculated as the ratio of weight (kg) to height (m) squared (kg/m^2).

MRI measurement

Cartilage volume of the right knee was assessed by MRI. Knees were imaged in the sagittal plane on a 1.5 T whole-body MR unit (Picker, Cleveland, OH, USA), and a fat-suppressed T1-weighted spoiled gradient-echo sequence was used. Knee cartilage volume was determined by means of image processing on an independent workstation as previously described[30,31]. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 mm (512 × 512 pixels). The volume of individual cartilage plates (medial tibial, lateral tibial, medial femoral, lateral femoral and patella) was isolated from the total volume of cartilage by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 μm × 312 μm and 1.5 mm thickness, continuous sections) for the final three-dimensional (3D) rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. The coefficients of variation (CV) obtained for cartilage volume measurements were 2.1–2.6%[31].

Knee femoral cartilage volume was determined using Cartiscope™ (ArthroVision Inc., Montreal, Canada) running on a Windows NT/9x workstation, as previously described[32–35]. Cartilage volume was evaluated directly from a standardized view of 3D cartilage geometry as the sum of elementary volumes. The CV was about 2%[34].

Cartilage defects on a 0–4 scale were graded at the medial and lateral tibial, medial and lateral femoral and patella sites as follows[36,37]: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface and bottom; grade 2 = irregularity on the surface or bottom and loss of thickness of <50%; grade 3 = deep ulceration with loss of thickness >50%; grade 4 = full-thickness chondral wear with exposure of subchondral bone. A cartilage defect had to be present in at least two consecutive slices and was defined as a score of ≥2 at any site measured at the knee (within that compartment). Intra-observer reliability expressed as intraclass correlation coefficient (ICC) was 0.89–0.94, and inter-observer reliability was 0.85–0.93[38].

Tibial bone area was determined at the medial and lateral compartments as previously described[24]. To transform the image from the sagittal to the axial plane, we used the Analyze Software package developed by the Mayo Clinic (Rochester, MN, USA). Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closet to

Table I
Characteristics of participants

	Nulliparous $N = 51$	Parous $N = 438$	P
Age (years)	62.3 (7.9)	62.0 (7.2)	0.79
Weight (kg)	71.8 (15.1)	71.6 (13.9)	0.94
Height (cm)	160.8 (6.4)	160.7 (6.0)	0.86
BMI (kg/m^2)	27.9 (6.4)	27.8 (5.3)	0.90
Smoked (%)	44	42	0.74
Steps (per day)	1429 (631)	1334 (490)	0.31
Ever used OC (%)	65	79	**0.02**
Current use of HRT (%)	32	42	0.34
Ever use of HRT (%)	64	62	0.84
Tibial cartilage volume (ml)	4.49 (0.84)	4.22 (0.81)	**0.04**
Femoral cartilage volume (ml)	7.00 (1.15)	6.82 (1.19)	0.35
Patella cartilage volume (ml)	2.80 (0.70)	2.65 (0.67)	0.15
Total knee cartilage volume (ml)	14.4 (2.22)	13.7 (2.04)	**0.04**
Tibial bone area (cm^2)	29.4 (2.7)	29.1 (2.4)	0.59
Tibial cartilage defects (%)	24	17	0.24
Femoral cartilage defects (%)	28	27	0.90
Patella cartilage defect (%)	27	46	**0.01**
Any cartilage defects (%)	49	56	0.34
JSN (%)	15	24	0.18
Osteophytes (%)	11	14	0.34

Data presented by mean and SD except where indicated. P values derived from unequal t test for continuous variables and chi^2 or Fisher's exact for dichotomous variables. Parous was defined as any live or still birth. JSN and defects defined as a score ≥2 and osteophytes defined as a score ≥1 at any site measured at knees including both left and right. Bold denote significant results.

Table II
The associations between parity, use of HRT, OC and radiographic OA

	JSN		Osteophytes	
	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Parity (yes/no)	1.76 (0.77, 4.07)	2.78 (0.75, 10.31)	1.40 (0.53, 3.68)	1.69 (0.59, 4.82)
Number of children				
Nulliparous ($n = 51$)	Reference	Reference	Reference	Reference
1–2 ($n = 194$)	1.60 (0.67, 3.84)	2.55 (0.64, 10.08)	1.33 (0.48, 3.68)	1.51 (0.36, 6.27)
3–4 ($n = 199$)	1.68 (0.70, 4.02)	3.02 (0.77, 11.89)	1.31 (0.47, 3.64)	1.81 (0.44, 7.41)
≥5 ($n = 45$)	**3.20 (1.14, 9.02)**	2.79 (0.61, 12.77)	2.17 (0.65, 7.27)	1.68 (0.35, 8.10)
P trend	0.05	0.17	0.30	0.47
Ever use of OC (ever/never)	0.48 (0.29, 0.78)	0.69 (0.34, 1.43)	**0.51 (0.29, 0.92)**	0.88 (0.38, 2.06)
Current use of HRT (current/never)	0.94 (0.52, 1.68)	1.25 (0.65, 2.41)	**0.42 (0.20, 0.91)**	0.49 (0.22, 1.12)
Ever use of HRT (ever/never)	1.02 (0.64, 1.63)	1.35 (0.81, 2.25)	0.58 (0.34, 1.00)	0.65 (0.36, 1.18)

JSN defined as a score ≥2 and osteophytes defined as a score ≥1 at any site measured at knees including both left and right. Bold denote significant results.
* Adjusted for age, BMI, smoking, parity, WOMAC-pain score, and use of OC and HRT where appropriate.

the knee joint. The bone area of the medial and lateral plateau was then directly measured from the reformatted axial images. The CV we obtained for these measurements were 2.2–2.6%.

X-ray measurement

A standing anteroposterior view of the right and left knee in a fixed semiflexed position was performed on all subjects at baseline and scored individually for osteophytes and joint space narrowing (JSN) on a scale of 0–3 (0 = normal and 3 = severe) according to the Osteoarthritis Research Society International atlas[39] as previously described[24]. The presence of osteophytes was defined as any score ≥1 whereas JSN was defined as any score ≥2 in the tibiofemoral compartments of either knee.

Statistical analysis

Unequal variance *t*-test was used to assess differences between parous and nulliparous for continuous characteristics whereas Chi^2 or Fisher's exact tests were used for categorical variables. Descriptive characteristics are presented as mean [standard deviation (SD)] or percentage. Cartilage volume was normally distributed. Univariable and multivariable linear regression analyses were employed to examine the associations between parity, use of HRT and/or OC and cartilage volume before and after adjustment for age, BMI, smoking, WOMAC-pain score and use of OC and/or HRT where appropriate. Confounders were selected based on our previous studies which identified age, BMI and smoking as important covariates and the observed differences between parous and nulliparous women in this study. Logistic regression analyses were used to investigate parity, use of HRT and OC, and the associations with presence of cartilage defects, JSN and osteophytes. All statistical analyses were performed on intercooled Stata 9.2 for windows (Statacorp, Texas, USA).

Results

There were 489 female participants aged 50–80 years (mean age 62 (±7.3) years, mean BMI 27.8 (±5.5) kg/m^2) who completed the questionnaires and had had MRI measured in the TASOAC study. Of these, 454 had a knee radiograph. Participants' characteristics are outlined in Table I. The majority of women were parous and most women had at some point used OC and/or HRT. Parous women were more likely to have been OC users, and to have lower tibial and total knee cartilage volume and a higher prevalence of patella cartilage defects than nulliparous women with no difference in the bone size and steps per day. Prevalence of JSN was 15%, 22%, 23% and 36% for each parity group from nulliparous to group 3 (≥5 children) respectively, whereas the prevalence of osteophytes for each group was 11%, 14%, 14% and 21%.

The associations between reproductive factors and radiographic OA are shown in Table II. Parous women had higher odds of both JSN and osteophytes compared with nulliparous, but none of these reached statistical significance. Use of OC and HRT was not significantly associated with either JSN or osteophytes after adjustment for confounders although users of either had generally lower odds of osteophytes.

The associations between parity and cartilage volume are shown in Table III. Compared with nulliparous women, parous women had lower total knee cartilage volume after adjustment for age, BMI,

Table III
The associations between parity, HRT, OC, total knee cartilage volume and cartilage defects

	Cartilage volume		Any cartilage defects*	
	Unadjusted β (95% CI)	Adjusted† β (95% CI)	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)
Parity (yes/no)	**−0.73 (−1.38, −0.08)**	**−0.69 (−1.34, −0.04)**	1.33 (0.74, 2.37)	1.42 (0.75, 2.71)
Number of children				
Nulliparous ($n = 51$)	Reference	Reference	Reference	Reference
1–2 ($n = 194$)	−0.59 (−1.28, +0.10)	−0.62 (−1.30, +0.07)	1.48 (0.80, 2.75)	1.61 (0.81, 3.20)
3–4 ($n = 199$)	**−0.73 (−1.41, −0.04)**	−0.68 (−1.36, +0.003)	1.13 (0.61, 2.08)	1.29 (0.65, 2.56)
≥5 ($n = 45$)	**−1.47 (−2.42, −0.52)**	**−1.07 (−2.04, −0.09)**	1.71 (0.76, 3.87)	1.25 (0.50, 3.14)
P trend	**0.01**	**0.04**	0.75	0.95
Ever use of OC (ever/never)	+0.17 (−0.33, +0.67)	−0.10 (−0.65, +0.45)	0.67 (0.43, 1.04)	0.98 (0.58, 1.66)
Current use of HRT (current/never)	+0.02 (−0.50, +0.53)	+0.03 (−0.48, +0.55)	0.66 (0.41, 1.05)	0.69 (0.42, 1.14)
Ever use of HRT (ever/never)	+0.35 (−0.07, +0.77)	+0.31 (−0.11, +0.73)	0.88 (0.60, 1.29)	0.99 (0.66, 1.49)

β: regression coefficient representing difference in mean cartilage volume (ml). Bold denote significant results.
* Any cartilage defects defined as a defect score of ≥2.
† Adjusted for age, BMI, smoking, parity, WOMAC-pain score, and use of OC and HRT where appropriate.

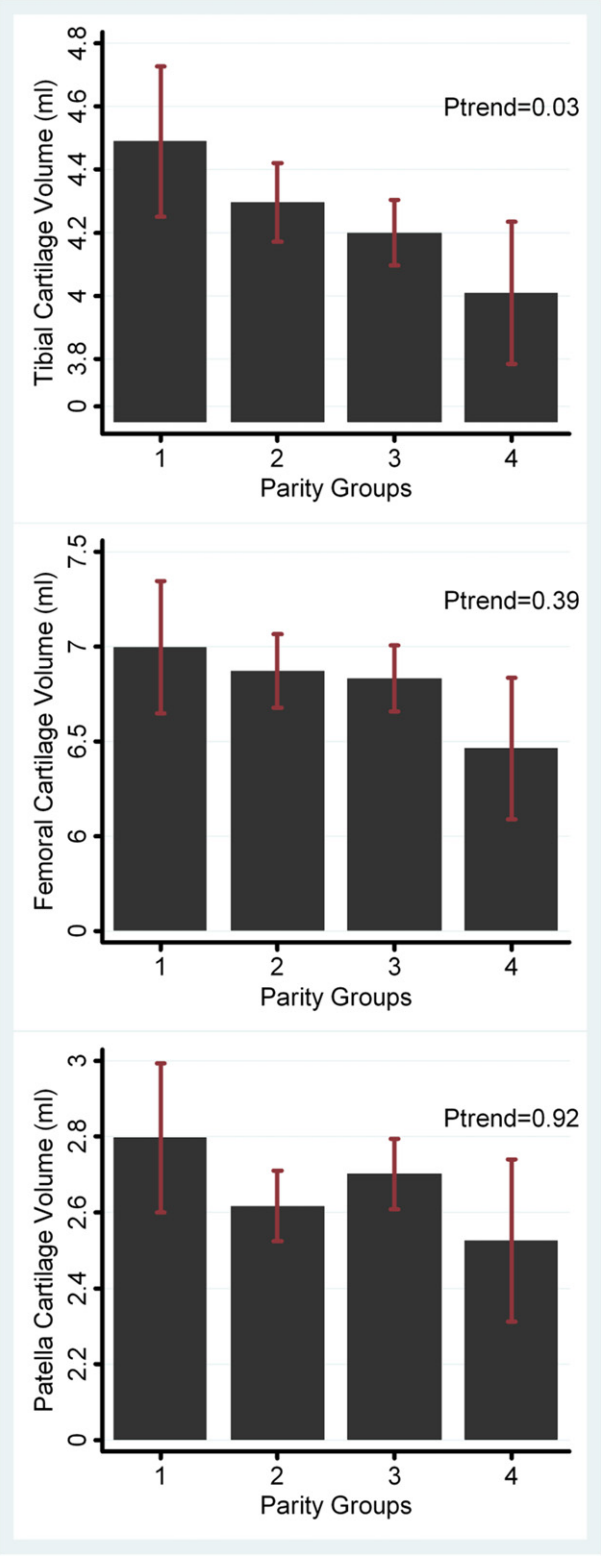

Fig. 1. Compartment specific cartilage volume by parity. *P* value adjusted for age, BMI, smoking, and use of OC and HRT. Group 1 = nulliparous. Group 2 = one to two children. Group 3 = three to four children. Group 4 = five or more children.

smoking, use of OC and use of HRT. Number of children had a linear association with decreasing cartilage volume in both the tibial compartment (Fig. 1) and total knee (Table III), and women who had five or more children had significantly lower cartilage volume

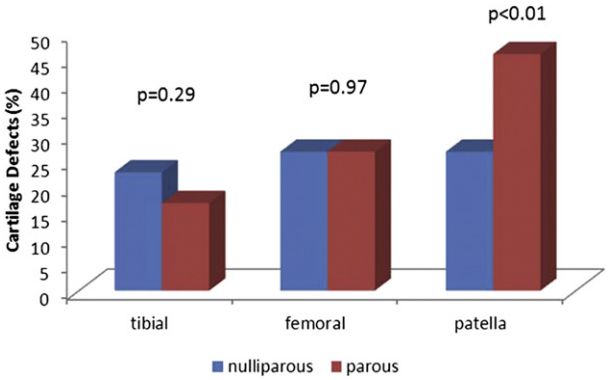

Fig. 2. Compartment specific cartilage defects by parity. *P* value was adjusted for age, BMI, smoking and use of OC and HRT.

compared with nulliparous women. Total cartilage volume decreased by 0.27 ml (95% CI = −0.52, −0.01) and tibial cartilage volume by 0.10 ml (95% CI = −0.20, −0.01) for each increasing parity group. Parity was also associated with increased odds of knee cartilage defects but only at the patella compartment (Fig. 2) which were significantly higher for parous women [adjusted odds ratio (OR) = 2.87, 95% CI = 1.39, 5.93].

Use of HRT was generally associated with modestly higher total knee cartilage volume and lower cartilage defects (Table III) but none of these differences were significant. OC use was not significantly associated with either cartilage volume or cartilage defects (Table III).

Age at menarche, breastfeeding, menopause and history of hysterectomy, were also assessed but had no association with any outcome measure (data not shown). The highest education level was associated positively with cartilage volume ($P = 0.02$) but not with parity ($P = 0.99$) whereas employment status was associated with parity ($P = 0.03$) but not cartilage volume ($P = 0.85$). Further adjustments for these two factors the associations between parity and cartilage volume were not changed (data not shown).

Knee surgery and WOMAC-pain score were not associated with parity or cartilage volume though they were both associated with cartilage defects and radiographic OA. Hand OA was negatively associated with cartilage volume but not associated with parity, cartilage defects or radiographic OA. Further adjustment for these three factors did not change the associations between parity and cartilage and radiographic OA in this study (data not shown). There was no association between parity and change in either cartilage volume or cartilage defects over 2.7 years (data not shown).

Discussion

In this cross-sectional population-based study, parity was independently associated with a lower cartilage volume in the tibial compartment and total knee, and higher cartilage defects in the patella compartment in older women. These results suggest parity may have an effect on the natural history of knee OA.

No previous studies have examined the associations between parity and knee cartilage. Studies of parity and the associations with clinical or radiographic OA or a risk of joint replacement are limited and have presented conflicting results[9,14–20]. Of the eight studies we identified, five studies showed no association with radiographic or symptomatic OA[14,16,17,19], one study presented a negative association with hand radiographic OA but not lower limb[18], and two studies reported positive associations with hand OA or joint replacement[9,15]. Differing findings between studies might be due to differences in the characteristics of study

participants (such as age), definitions of OA, site measured or the ability to adjust for confounders. In our study, knee OA was assessed by radiography with no significant associations with reproductive factors found which is consistent with most of the above studies. However, MRI measurements had a number of significant associations examining parity as both a dichotomous variable and as number of children, suggesting radiographic OA is much less sensitive than MRI assessment. There was some variation between sites with parity being associated with tibial cartilage volume and patella cartilage defects. This is largely unexplained. However, cartilage defects and cartilage volume loss may not necessarily appear together in the same OA knee compartment as cartilage defects assess focal lesions whereas cartilage volume provides a more global evaluation of cartilage loss in an entire compartment. The association between parity and cartilage defects could be real as it fits with the overall cartilage volume effect. However, it could also be a chance association.

We have further examined the follow-up data of cartilage volume and the defects and found that parity was not associated with either cartilage volume change or change in cartilage defects. This might be expected given that pregnancy was an exposure in the relatively distant past.

The mechanism underlying the association between parity and cartilage is not clear. There are several possibilities including alterations in sex hormones, weight gain, loading on the knee (weight gain and baby carrying) and change in lifestyle which includes increased household chores or a reduction in recreational physical activity during the period of pregnancy and breastfeeding. The levels of both estrogen and progesterone increase during pregnancy[12] and the receptors for both hormones have been found in human cartilage[40,41]. Most women gain weight during pregnancy and a weight gain of 11–15 kg is recommended for normal weight women (BMI 19.8–26.0 kg/m^2) to achieve optimal fetal and maternal outcomes[13]. Weight gain may also persist after birth increasing the load to the knee. While we have adjusted for current weight, we did not assess weight gain during pregnancy as this would likely be subject to considerable recall error given the age of our participants. Women with high parity may have a lower socioeconomic status with more household chores thus this may be another potential mechanism underlying the associations. However further adjustment for highest education level achieved and employment status did not change the associations between parity and cartilage.

There is evidence that ERT may have a protective effect on radiographic OA in postmenopausal women[42,43]; however, limited studies have explored the effect of sex hormones on cartilage. A cross-sectional study of 81 participants found that users of ERT for 5 or more years had more tibial knee cartilage volume than non-users[25] but this association was not present for patella cartilage volume[26], and a longitudinal analysis of 57 participants from the same sample found no association between ERT and change in tibial cartilage volume over 2.5 years of follow-up[27]. Our study with a relatively large number of participants is most consistent with little or no effect of HRT on either MRI or radiographic measurements of cartilage. Similarly, OC use and duration were not associated with cartilage health although OC use is associated with bone mass and vertebral deformity in these women[21].

One of the important limitations of this study is that several factors assessed by questionnaire are subject to recall. However, responses to questions relating to parity and current use of HRT would be considered highly accurate. It is likely that, any misclassification would be no-differential thus would shift our results toward the null as reproductive history was assessed at the same time as clinical measurements. We assessed radiographic OA at the tibiofemoral compartment only therefore we cannot address any association with patellofemoral radiographic OA. We have taken still birth into account when assessing parity but twins or triplets were not assessed in this study so may potentially result in misclassification of women by parity group. However the number of multiple births is likely to be very small and misclassification would likely to result in an underestimation of the association if the number of pregnancies is over estimated. Another limitation is the cross-sectional design, which does not allow testing of causal pathways, although births occurred many years prior to assessment of cartilage, and there was a dose response association suggesting a biologically plausible association.

In conclusion, parity (but not use of HRT or OC) is independently associated with lower cartilage volume primarily in the tibial compartment and higher cartilage defects in the patella compartment in this population-based sample of older women.

Author contributions

Conception and design: SW, AV, GJ.
Acquisition of data: SW, JMP, JPP, FA, GJ.
Analysis and interpretation of data: SW, AV, CD, GJ.
Drafting the article or critical revision: SW, AV, CD, JMP, JPP, FV, GJ.

Role of the funding source

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Conflict of interest

The authors have no conflicts of interest to declare.

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